

Osteogenesis Imperfecta Type II: Fetal Magnetic Resonance Imaging Findings

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Key Words

Osteogenesis imperfecta • Fetal magnetic resonance imaging • Magnetic resonance fetography • Prenatal diagnosis

Abstract

We describe the prenatal magnetic resonance imaging (MRI) findings in a 25-week-old fetus with proven osteogenesis imperfecta type II. Fetal MRI findings are correlated with prenatal ultrasonography, conventional x-ray fetography and postpartal findings. Fetal MRI proves to be superior to conventional fetography in the evaluation of the skeletal findings. The high soft tissue resolution, the large field of view and the multiplanar imaging make it possible to study the non-ossified fetal skeleton in detail. Compared to prenatal ultrasonography, fetal MRI gives important additional information about the expected lung functionality by estimating fetal lung volume and signal intensity and rules out possible additional abnormalities of major fetal organs. These parameters may serve as valuable, additional prognostic markers in the prenatal diagnostic work-up.

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Introduction

Osteogenesis imperfecta (OI) or brittle bone disease, first described by Ekman in 1788, is a heterogeneous group of inherited connective tissue disorders characterized by an increased bone fragility and low bone mass [1]. OI results from either a reduction of the normal type I collagen production (mildest form, type I OI) or from an abnormal collagen type 1 synthesis.

Four different types of OI are distinguished [2, 3]. Type I is the most frequent form (>60% of patients). Clinical symptoms are usually mild; children rarely suffer from skeletal deformities, hearing loss often occurs (50% of families). Type II is the most severe, invariable lethal form. The main death courses are severe bone fragility, complications from infection in hypoplastic lungs, respiratory distress syndrome, cardiac insufficiency, or cerebral injury. Children with type III and IV OI who survive the neonatal period suffer however from significant complications. Recently, a type V and VI as well as a rhizomelic OI have been identified by clinical and molecular analysis [3, 4].

Prenatal ultrasonography (US) is the first modality of choice for detecting fetal pathologies including OI. Magnetic resonance imaging (MRI) serves as a second-line imaging modality to confirm, correct or complete US findings [3, 5, 6]. Fetal MRI is especially advantageous

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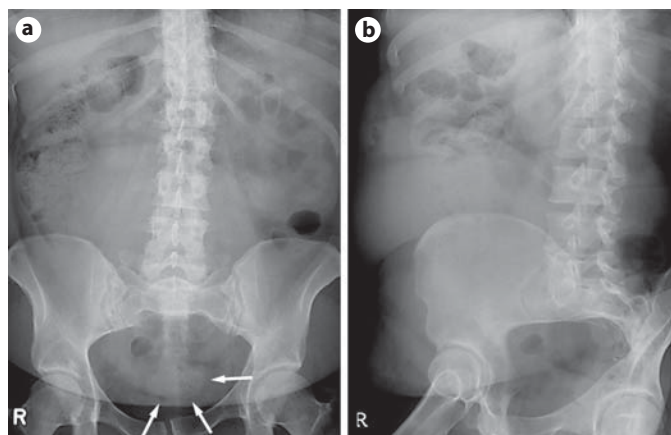


Fig. 1. Conventional AP and lateral oblique fetography: The fetal skull can be faintly delineated within the maternal pelvis (arrows). The remainder of the fetal skeleton is too osteopenic to be delineated: 'invisible fetus' phenomenon.

because of its high spatial and soft tissue resolution, the high T_2 contrast between fluid and solid tissue, the large field of view and the absence of obscuring maternal bowel gas or pelvic bony structure artifacts [7]. During the last decade, molecular diagnosis including structure analysis of collagen molecules in cultured fibroblasts obtained from chorion villus sampling and amniocytes as well as genomic DNA screening has become a useful tool in the diagnostic work-up of suspected skeletal dysplasia. These tests are however not widely available and time-consuming.

We present the prenatal fetal MRI findings in a case of OI type II. Fetal MRI findings are correlated with prenatal conventional fetography (CF) and postnatal findings.

Case Report

A 37-year-old primigravida woman was referred to our hospital for CF and possible fetal MRI because routine prenatal US examination at 24 weeks' gestation had suspected skeletal dysplasia. US findings included reduced acoustic shadowing, bowing and shortening of the long bones and a small fetal chest circumference. Differential diagnosis included thanatophoric dwarfism and OI. No additional fetal pathology was identified.

The family history was uneventful, pregnancy was unremarkable. The mother was healthy and denied being exposed to drugs relevant to the pregnancy.

CF showed a small osteopenic skull. The degree of skeletal osteopenia was so severe that CF failed to delineate the remainder of the fetal skeleton. This phenomenon is also known as 'the invisible fetus' appearance (fig. 1).

Because CF failed to establish a definite diagnosis, ultrafast fetal MRI was performed using a 1.5-T MRI unit (Signa Excite II, General Electric Healthcare, Milwaukee, Wisc., USA). Imaging was acquired according to the routine departmental protocol. A multiplanar T_2 -weighted single-shot fast spin-echo as well as T_1 -weighted gradient echo sequences of the fetus were acquired using an 8-channel phase array cardiac surface coil [8]. No maternal or fetal sedation was administered. The entire fetus, placenta and maternal uterus were studied.

MRI revealed significantly shortened and bowed extremities with normal hands and feet (fig. 2a, b). The thorax was small in size with a dumbbell shape. The volumetric measurements of the fetal lungs, using a previously published method, showed significantly reduced lung volumes (9.1 ml) (28% of the expected, age-corrected lung volume: 32.9 ml) [9]. In addition, the T_2 signal intensity was significantly reduced indicating lung hypoplasia (fig. 2a, b). No additional abnormalities were seen: the brain, spinal cord, vertebral column and abdominal organs were unremarkable. The amount of amniotic fluid was normal. The placenta and umbilical cord were normal in size without any pathology.

Based on the fetal MRI findings in combination with the 'invisible fetus' appearance on CF, OI type II was postulated. Prognosis was estimated as being poor. The parents were informed about the suspected diagnosis and counseled about the likely lethal outcome. The parents decided to terminate pregnancy which was performed 1 week later during the 25th week of gestation.

Post-mortem examination (autopsy) confirmed prenatal diagnosis. Macro- and microscopic inspection showed significant growth retardation, multiple fractures of the long bones and ribs, hypermobility of the elbows and hip joints as well as a significant lung hypoplasia (fig. 3a, b). Postnatal conventional radiography showed the classical features of type II OI with deformation of all extremities due to multiple fractures as well as a small, narrowed, dumbbell-shaped thorax (fig. 4), triangular face with beaked nose, and typical frog-like position. Chromosomal analysis revealed a 46,XX karyotype without chromosomal abnormalities.

Discussion

OI is a group of inherited connective tissue disorders where the basic pathology is defective collagen maturation. The incidence of OI varies from 1 in 20,000 to 1 in 60,000 and is more common in female fetuses [2, 10]. In the vast majority of cases (95% of patients with definite diagnosis), OI is caused by dominant mutations in the gene encoding for the type I procollagen (COL1A1 and COL1A2). In the meantime, more than 400 different causal mutations have been published and reported in the Human Type I Collagen Mutation Database (www.le.ac.uk/genetics/collagen/index.html) [11, 12].

Individuals with OI have a 25% (type II, III) to 50% (type I, IV) chance of transmitting the disease to their offspring and therefore genetic counseling and prenatal diagnosis should be offered to all affected patients. The

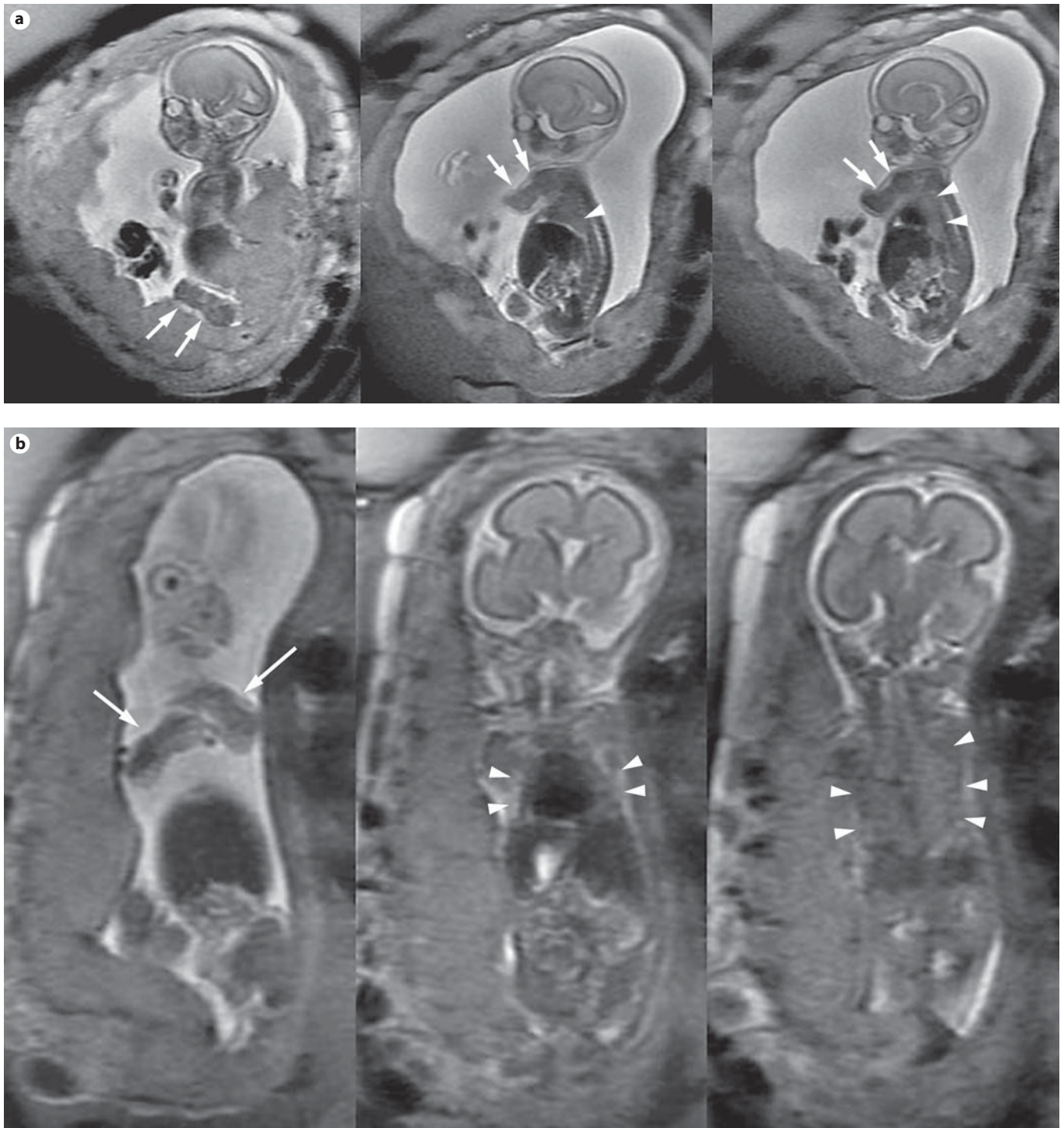


Fig. 2. a Sagittal T₂-weighted single-shot fast spin-echo MR images of the fetus: the shortened and widened long bones are easily identified within the upper and lower extremities (arrows). In addition, the fetal lungs are small in size and significantly T₂-hypointense (arrowheads) indicating lung hypoplasia. The remainder of the fetal anatomy is without pathology. The images have

been flipped top to bottom. **b** Coronal T₂-weighted single-shot fast spin-echo MR images of the fetus: the shortened and widened long bones are easily identified within the upper extremities that are folded in front of the fetus (arrows). In addition, a small dumb-bell-shaped thorax with T₂-hypointense and small lungs are displayed (arrowheads).



Color version available online



Fig. 3. a, b Post-mortem examination of the fetus confirms shortened and bowed upper and lower extremities. The chest volume is too small. The fetus is in the typical 'frog-like' position.

risk of recurrence in healthy parents who have an affected offspring arises from parental germline mosaicism and is estimated at 5–8% [13–15].

Skeletal manifestations result from a generalized deficiency of membranous and endochondral bone develop-

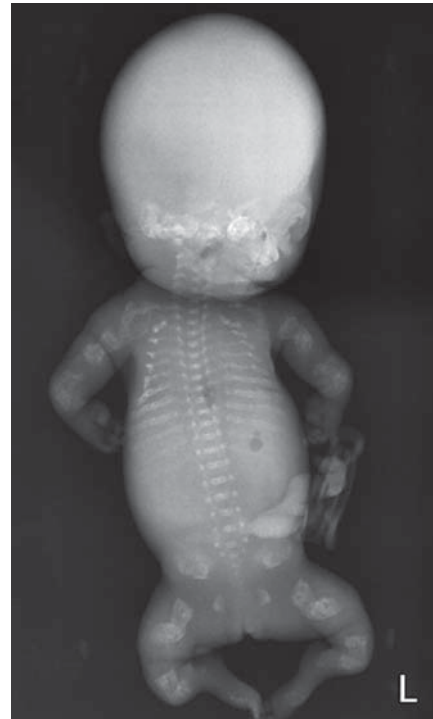


Fig. 4. Post-mortem conventional AP fetography: multiple fractures are seen along the widened, bowed and deformed long bones of the upper and lower extremities. In addition, multiple fractures are seen within the ribs with resulting small chest volume and hypoplastic lungs. The entire fetal skeleton is significantly osteopenic.

ment due to abnormal collagen production and include markedly thinned calvarium with delayed closure of fontanelles, sutures and excessive wormian bone formation resulting in the brittleness of OI bone. The most frequent extraskelletal manifestations include the blue sclerae, dentinogenesis imperfecta, hyperlaxity of the ligaments, and progressive hearing loss. The spectrum of the disease varies widely: children may present with only a mild osteoporosis (type I OI), while the most severe cases may be lethal early within the neonatal period (type II OI).

According to the most widely used classification [16], OI is classified into four types: type I–IV. Recently, OI type V, VI and rhizomelic OI have been added to the classification (table 1) [3, 11]. These additional types of OI have been identified on the basis of recent clinical and molecular findings. OI is also grouped into two classes: deforming and non-deforming bone disease. This arbitrary grouping can be helpful for correlating clinical phenotype with underlying genetic and pathophysiological findings [17].

Table 1. Classification of OI [1, 4–6, 11]

Molecular classification	Clinical classification	Clinical severity	Fracture frequency	Dentinogenesis imperfecta	Hearing loss	Sclera's color
Dominant negative	type II	perinatal, lethal progressive	++++	-/+	+	intensive blue
Dominant negative	type III	deforming moderate	+++	-/+	+	light blue
Dominant negative	type IV	deforming moderate	+ / ++	-/+	+	white
?	type V	deforming moderate to severe	++ / +++	-/+	–	white/faintly blue
?	type VI	deforming moderate to severe	++ / +++	–	–	white/faintly blue
?	rhizomelic OI	deforming	++ / +++	–(?)	–(?)	(?)
Haploid insufficiency	type I	classical mild OI	-/+	-/+	+++	intensive blue

Type II OI is the most severe, invariable lethal form of OI. Most children die within the perinatal period. Death usually occurs in the neonatal period due to complications from infection, respiratory distress, cardiac insufficiency, or cerebral injury [6]. Newborns present with soft calvarian bones, peculiar triangular-shaped face with a beaked nose and blue sclera [6]. Clinical examination usually shows short, deformed extremities due to multiple fractures and a typical ‘frog-like’ position. In addition to the well-defined skeletal anomalies in type II OI, associated central nervous system (CNS) findings have been shown including vascular microcalcifications and migrational defects [2, 18].

Diagnosis of OI as early as possible during pregnancy is essential to guide pregnancy and to counsel parents. Molecular testing procedures, such as RNA and protein analysis of fibroblasts and genomic DNA analysis from extracted blood, are available to identify the presence of mutation and may prove beneficial in the prenatal diagnosis of the lethal OI (type II) as well as in the evaluation of the milder OI type I cases. Molecular testing may also be beneficial if child abuse is suspected. However, up-to-date molecular diagnosis is not available in every institution and the screening of type I collagen genes cannot cover the whole clinical range of OI since the recently described forms (type V, VI, rhizomelic OI) have their causal mutations in yet unknown loci.

Currently, prenatal screening and diagnosis of OI is based on the so-called characteristic sonographic and radiological findings.

In the absence of a previous history of OI, fetal morphological examination by prenatal US remains the screening method of choice for antenatal diagnosis of OI.

Sonographic features include a reduced acoustic shadowing of long bones, marked bowing and shortening of

long bones and an increased nuchal translucency in early pregnancy [5]. First trimester prenatal diagnosis of isolated OI has been reported as early as 12–14 weeks of gestation [19]. Although the sensitivity of US performed at 18–22 weeks of gestation for detecting lethal skeletal dysplasia is estimated as being high (94–96% and 70% for detection of the major limb abnormalities), it is of limited value to provide the accurate diagnosis (30–50%) [20]. Despite the fact that several sonographic criteria (e.g. presence of shortened, curved femora and a small chest) have been used to distinguish the non-lethal forms from the lethal of skeletal dysplasia (including OI type II), a significant proportion, 7.8% of fetuses with prenatally established skeletal dysplasia, are misdiagnosed [21]. US is also limited in the detection of the mild forms of OI and the detailed evaluation of additional abnormalities, especially in the identification of the degree of associated pulmonary hypoplasia, which may determine prognosis [10, 22].

Recent studies have suggested the potential advantage of using three-dimensional US to improve the accuracy of prenatal diagnosis. Three-dimensional US suffers however from the well-known limitations of US which include unfavorable fetal position, maternal obesity, obscuring pelvic bones and maternal bowel gas and the limited field of view [6]. In addition, three-dimensional prenatal US cannot give adequate information about the maturation of the fetal lungs.

Conventional radiography (fetography), initially used for the antenatal diagnosis of OI, is nowadays rarely used. The main conventional radiological features are bowing (camptomelia) and shortening of the limbs and narrowing of the thorax due to multiple rib fractures. Extreme radiolucency of the fetal skeleton may result in the radiological phenomenon of an ‘invisible fetus’ [3, 12].

Ruando et al. [23] reported the usefulness of helical computer tomography in OI diagnostics, which can provide detailed information about the abnormal bone matrix, density and shape. A major limitation of CT is however the exposure of the fetus to a significant amount of ionizing radiation (up to 3 mGy) [24]. Ultrafast MRI is a relatively new imaging modality that makes it possible to study fetal anatomy in high detail without the use of ionizing radiation. The short acquisition times allows to 'picture freeze' the fetus without the need for fetal sedation. Multiple studies have shown the value of fetal MRI in the prenatal evaluation of complex CNS pathologies. In addition, fetal MRI is progressively used for the evaluation of the fetal thorax and abdomen. Fetal MRI serves as a complementary imaging tool to prenatal US; it is especially advantageous compared to prenatal US because of its high spatial resolution, the high T₂ contrast between fluid and solid tissue, the large field of view and that imaging is not obscured by maternal bowel gas, maternal obesity or overlying pelvic bony structures [7]. In particular, fetal MRI provides reliable information concerning the survey of the internal organs including the CNS, detecting associated anomalies or abnormal brain maturation, and allows to analyze lung development and functionality using fetal lung volume measurements [25, 26]

and the MR signal characteristics of the lungs [27, 28]. Fetal MRI can be used to confirm, correct or complete US findings. However, only a few studies are currently available that describe the imaging findings of fetal MRI in the prenatal diagnosis of OI type II [2, 10]. Teng et al. [10] suggested that fetal MRI at the beginning of the second trimester is more valuable than prenatal US in the evaluation of OI.

In our experience, fetal MRI is a valuable adjunct to prenatal US in the diagnosis of OI type II. Fetal MRI clearly demonstrated the multiple fractures and deformation of long bones and ribs. Quantification of the fetal lung volume and evaluation of the lung signal characteristics can be used to determine a prognosis for fetal survival [25, 26]. Fetal lung hypoplasia was confirmed by postpartal autopsy findings in our case. Conventional fetal radiography is only of very limited value. It uses ionizing radiation and does not give reliable information about the degree of lung hypoplasia [2, 10].

In conclusion, we recommend adding fetal MRI to prenatal US in those cases where prenatal US cannot differentiate between OI and other forms of skeletal dysplasia. In addition, fetal MRI provides important prognostic information about possible associated fetal abnormalities and the degree of lung hypoplasia.

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